REMARKS

In the Office Action dated January 18, 2008, claims 45-46, 49-55, 60-65, 68-71 and 87-91 are pending and under consideration. Claims 45-46, 62, 63, 64, 71, 87, 88, and 89 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Itskovitz-Eldo et al. (Molecular Medicine 6(2): 88-95, February 2000) (hereinafter " Itskovitz-Eldor"). Claims 45-46, 49-55, 60-65, 68-71, and 87-91 are rejected under 35 U.S.C. §103(a) as unpatentable over Itskovits-Eldor in view of Sugi et al., Developmental Dynamics 200: 155-162, 1994 ("Sugi"), Zhu et al., Developmental Dynamics 207: 429-438, 1996 ("Zhu"), Lough et al., Developmental Dynamics 217: 327-342, 2000 ("Lough"), and Klug et al., J Clin Invest 98: 216-224 1996 ("Klug"). Claims 45-46 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claim 1 of Serial No. 11/644,790.

This Response addresses each of the Examiner's rejections. Applicant therefore respectfully submits that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Rejection Under 35 U.S.C. §102(b)

According to the Examiner, Itskovitz-Eldor teaches a method for inducing differentiation of an undifferentiated human embryonic stem (hES) cell into embryoid bodies (EBs) by culturing the hES cell in the presence of a mouse embryonic stem cell. The EBs allegedly show characteristic regional expression of embryonic markers specific for different lineages, namely, ζ-globin (mesoderm), neurofilament 68Kd (ectoderm) and α-fetoprotein. The Examiner contends that such disclosure anticipates instant claims 45 and 88.

Further according to the Examiner, Itskovitz-Eldor also teaches obtaining a cell population comprising a subpopulation of differentiated cells of a mesodermal lineage, wherein

the differentiated cells are derived from undifferentiated hES cells, by culturing the hES cells in the presence of a mouse embryonic stem cell under conditions that induce differentiation of the undifferentiated hES cell into the mesoderm cell, wherein the human hEBs show characteristic regional expression of embryonic markers specific for different lineages. The Examiner contends that such disclosure anticipates claims 46 and 88.

Applicant respectfully disagrees with the Examiner's rejection. The Examiner's characterization of the reference is inaccurate. In Itzkovitz-Eldor, the hES cells are co-cultured with embryonic (fibroblast) cells which are used to maintain the cells in an undifferentiated state. Once the embryonic fibroblast cells are removed, the undifferentiated hES cells proceed to differentiate to form embryoid bodies. See page 89, 2nd column. Therefore, it is not until the hES cells are transferred do they differentiate, and by then the embryonic cells are removed. Thus, Applicant submits that the hES cells are ***not*** co-cultured with embryonic cells (fibroblasts) to induce differentiation, as presently claimed. See instant claim 45, for example. In fact, in Itskovitz-Eldor, the fibroblasts are necessary to maintain the hES cells in an undifferentiated state.

Hence, Applicant respectfully submits that Itskovitz-Eldor does not teach the co-culture of the hES cells and an embryonic cell to induce differentiation of the hES cells into mesoderm cells, as presently claimed. The rejection of 45-46, 62, 63, 64, 71, 87, 88, and 89 under 35 U.S.C. §102(b) based on Itskovitz-Eldo is therefore overcome and withdrawal thereof is respectfully requested.

Rejection Under 35 U.S.C. §103

The Examiner's rejection begins with a description of the Itskovitz-Eldor reference. The Examiner contends that Itskovitz-Eldor differs from the present invention for failing to

teach that the embryonic cell is an endodermal or ectodermal cell or tissue. However, the Examiner contends that Sugi teaches the effect of co-culturing of anterior endoderm and mesoderm cells on terminal differentiation of cardiomyocytes *in vitro*. Therefore, the Examiner concludes that Sugi provides sufficient motivation for one of ordinary skill in the art to apply the endodermal embryonic cells of Sugi into the hES cells culture system of Itskovitz-Eldor for inducing differentiation of an undifferentiated hES cell. The Examiner also states that it would have been obvious for one skilled in the art to modify the conditions of Itskovitz-Eldor, by co-culturing hES cells with mesodermal, endodermal cells or both to induce terminal differentiation of the undifferentiated hES cells, as taught by Sugi. The additional references to Zhu, Lough and Klug are relied upon by the Examiner in rejecting certain dependent claims, which include features not disclosed or suggested by the combination of Itskovitz-Eldor and Sugi.

In the first instance, Applicant respectfully submits that Itskovitz-Eldor fails to provide the necessary teaching as a primary reference to form a basis for combining with other references. As submitted above, the co-culture of the hES cell and the mouse embryonic (fibroblast) cell does not induce differentiation, and does not represent a condition that induces differentiation, of the undifferentiated hES cell into a mesoderm cell. The co-culture of hES cells with the mouse embryonic cell (fibroblast) is to ensure that the hES cells maintain their undifferentiated state. It is not until the hES cells are removed from the co-culture that embryoid bodies cells are formed. See, e.g., on page 89, 2nd column of the reference, it is stated that "*To induce formation of EBs, ES cells were transferred using collagenase...*" Therefore, Itzkovitz-Eldor does not teach the use of a co-culture system to *induce* the hES cells to differentiate into a mesodermal cell.

Further, Applicant respectfully submits that these fundamental deficiencies of Itzkovitz-Eldor are not cured by the secondary reference to Sugi, as Sugi does not teach differentiation of an undifferentiated human stem cell to a mesoderm cell. Rather, Sugi teaches differentiation of a mesoderm cell to a terminally differentiated cardiomyocyte. In fact, Sugi's teaching is directed to the effect of endodermal cells on the terminal differentiation of mesodermal cells into cardiac myocytes. Hence, Sugi is a citation that relates to a different stage of the differentiation process.

The Examiner contends that Sugi provides sufficient motivation for one of ordinary skill in the art to apply the endodermal embryonic cells of Sugi into the hES cell culture system of Itzkovitz-Eldor for inducing differentiation of an undifferentiated hES cell.

Applicant respectfully disagrees with the Examiner's contention. Sugi's teaching is directed to the effect of endodermal cells on the terminal differentiation of mesodermal cells into cardiac myocytes. There is no teaching or suggestion in Sugi for whether endodermal cells would have any impact on undifferentiated cells, such as undifferentiated hES cells, which are the starting cells of the presently claimed methods. Therefore, the Examiner's contention that Sugi provides sufficient motivation for one to apply the endoderm cells to hES cells is completely unsupported.

In this connection, Applicant respectfully directs the Examiner's attention to the Sugi reference, on page 158, first column, where it is stated that cardiogenic effects of anterior endoderm appear to be specific to a specific cell population, shown by the inability of posterior endoderm or anterior ectoderm cells to support cardiogenesis as evidenced by an absence of contractility and sarcomeric actin staining. Furthermore, in the second column of the same page (page 158), it is stated that the finding that anterior, but not posterior, mesoderm from

stage 6 embryos undergoes endoderm-stimulated cardiogenisis suggests that cells in the heart-forming region (HFR) must be pre-specified for the cardiogenic lineage. Hence, once the cell is differentiated to the mesoderm state, it is pre-specified for the cardiogenic lineage and the anterior endoderm appears to be specific for supporting the cardiogenesis of that cell type.

The hES in the present invention are undifferentiated and not pre-specified for the cardiogenic lineage. Applicant submits that based on Sugi's disclosure, those skilled in the art would not have had any expectation of success that such undifferentiated hES cells, which do not have a pre-specification, would proceed down the cardiogenic path, let alone when these hES cells are co-cultured with cells which in Itzkovitz-Eldor were used to maintain the hES cells in an undifferentiated state.

Applicant further respectfully submits that the combination of Itzkovitz-Eldor and Sugi is also improper because the two citations are contrary to each other insofar as the use of the endoderm or ectoderm cell is concerned. Itzkovitz-Eldor teaches that use of such cell will maintain the hES cells in an undifferentiated state, while Sugi teaches that the endoderm or ectoderm cell is instrumental to the cardiogenic pathway (of a mesoderm cell).

Therefore, it is respectfully submitted that the combination of Itzkovitz-Eldor and Sugi falls short in suggesting the presently claimed invention. It is further respectfully submitted that the deficiencies of the combination of Itzkovitz-Eldor and Sugi are not cured by the additionally cited references. Moreover, Applicant observes that Zhu and Lough both relate to the terminal differentiation of mesoderm cells to cardiomyocytes. Therefore, these citations are not relevant to the differentiation of hES cells or of any other unspecified undifferentiated cells.

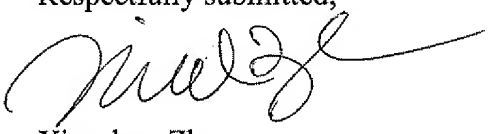
Therefore, Applicant respectfully submits that the presently claimed invention, as a whole, is not obvious over the cited references. Withdrawal of the rejection of 45-46, 49-55, 60-65, 68-71, and 87-91 under 35 U.S.C. §103(a) is respectfully requested.

Claims 45-46 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claim 1 of Serial No. 11/644,790. The Examiner contends that both sets of claims are directed to induction of differentiation of undifferentiated cells.

Applicant respectfully submits that claim 1 of the '790 application relates to a method of inducing cardiomyocyte differentiation of a stem cell by culturing the stem cell in the presence of a prostaglandin, analogue or functional equivalent thereof alone or in combination with essential minerals, small molecules and protein growth factors of the FGF, IGF and BMP families. Claim 1 of the '790 patent does not teach or suggest culturing a hES cell in the presence of an embryonic cell and/or extracellular medium of an embryonic cell to induce differentiation of the hES cell, as presently claimed. As such, the present claims are patentably distinct over claim 1 of Serial No. 11/644,790. Withdrawal of the double patenting rejection is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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